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Persistent symptoms following SARS-CoV-2 infection among children and young people: a meta-analysis of controlled and uncontrolled studies.

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Abstract

Background: Data on the long-term impact of SARS-CoV-2 infection in children and young people (CYP) is conflicting. We assessed evidence on long-term post-COVID symptoms in CYP examining prevalence, risk factors, type and duration.

Methods: Systematic search of published and unpublished literature using 13 online databases between 01/12/2019 – 31/07/2021. Eligible studies reported CYP ≤19 years with confirmed or probable SARS-CoV-2 with any symptoms persisting beyond acute illness. Random effects meta-analyses examined pooled risk difference in symptom prevalence (controlled studies only) and pooled prevalence (uncontrolled studies also included). Meta-regression examined study characteristics hypothesised to be associated with symptom prevalence. Prospectively registered: CRD42021233153.

Findings: Twenty two of 3357 unique studies were eligible, including 23,141 CYP. Median duration of follow-up was 125 days (IQR 99-231).

Pooled risk difference in post-COVID cases compared to controls (5 studies) were significantly higher for cognitive difficulties (3% (95% CI 1, 4)), headache (5% (1, 8)), loss of smell (8%, (2, 15)), sore throat (2% (1, 2)) and sore eyes (2% (1, 3)) but not abdominal pain, cough, fatigue, myalgia, insomnia, diarrhoea, fever, dizziness or dyspnoea.

Pooled prevalence of symptoms in post-COVID participants in 17 studies ranged from 15% (diarrhoea) to 47% (fatigue). Age was associated with higher prevalence of all symptoms except cough. Higher study quality was associated with lower prevalence of all symptoms, except loss of smell and cognitive symptoms.

Interpretation: The frequency of the majority of reported persistent symptoms was similar in SARS-CoV-2 positive cases and controls. This systematic review and meta-analysis highlights the critical importance of a control group in studies on CYP post SARS-CoV-2 infection.

Funding: None

Research in context

Evidence before this study

While there has been much recent interest in persistent symptoms in children and young people (CYP) post SARS-CoV-2 infection, the majority of studies to date have been open to significant bias. The lack of a control group in many studies has made it hard to separate symptoms due to infection from those due to the pressures of a pandemic. Prior to our study, a search of Medline, Cochrane, medRxiv and PROSPERO identified one published narrative review and no meta-analyses specifically examining persistent symptoms in children and young people following SARS-CoV-2 infection.

We systematically searched published and unpublished literature using 13 online databases on 31/07/2021 to identify studies reporting symptoms in CYP ≤19 years persisting beyond acute SARS-CoV-2 infection. Although all studies were analysed, our meta-analysis primarily focused on pooled risk difference in symptom prevalence in controlled studies (with SARS-CoV-2 negative CYP).

Added value of this study

We did a systematic review of 22 studies from 12 countries including 23,141 CYP. We found that although the pooled prevalence of symptoms across all studies was high, when we restricted our meta-analysis to only those with a SARS-CoV-2 negative control group, most reported persistent symptoms were equally common in SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Higher study quality was associated with lower prevalence of all symptoms, except loss of smell and cognitive symptoms.

Small but significant increases in the pooled risk difference were seen for cognitive difficulties (3% (95% CI 1, 4)), headache (5% (1, 8)), loss of smell (8%, (2, 15)), sore throat (2% (1, 2)) and sore eyes (2% (1, 3)) in CYP following confirmed SARS-CoV-2 infection compared to negative controls.

Implications of all the available evidence

To the best of our knowledge, this is the first study to systematically review and meta-analyse persistent symptoms following SARS-CoV-2 infection in CYP. Our study shows that estimates of symptom prevalence are considerably lower in controlled studies highlighting the critical importance of a control group in studies on CYP post SARS-CoV-2 infection.

Introduction

Children and young people (CYP) are more likely to be asymptomatic or develop a mild, transient illness following SARS-CoV-2 infection compared to adults, whose risk of severe COVID-19, hospitalisation and death increases with age. Whilst most CYP recover quickly, a small proportion may have on-going symptoms persisting for weeks to months after SARS-CoV-2 infection.

There are a number of terms in use to describe post-COVID symptoms. "Long-COVID" is a term created by patients in May 2020 as a hashtag on social media outlet Twitter. [1,2] Other descriptions include "long-haul COVID", "Post COVID-19 syndrome", "Chronic COVID syndrome (CCS) and "post-acute sequelae of COVID-19 (PASC), the latter a term mostly used in the United States (US). [3-5] Persistent post-COVID symptoms are emerging as a broad spectrum of manifestations in adults and CYP. The syndrome has been described as a complex multisystem disease appearing during the typical convalescence phase of illness, with persistent, heterogenous and recurring symptoms which may wax and wane, lasting beyond four weeks from the date of SARS-CoV-2 infection. [6,7] There is no universally accepted standardised case definition of the syndrome, but despite this lack of consensus, different categorisations are emerging. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) working guidelines have developed terminology that can be used to describe post COVID-19 syndrome.[4] "Ongoing symptomatic COVID-19" is defined as signs and symptoms that persist between 4 and 12 weeks from onset of the infection and "Post COVID-19 syndrome" is defined as signs and symptoms persisting beyond 12 weeks from the date of onset.[4] Alternatively, the US Centres for Disease Control and Prevention (CDC), define "Post COVID-19 Conditions" as an umbrella term for a wide range of health consequences that are present more than four weeks after acute infection.[8] Furthermore, the UK National Institute for Health Research (NIHR) has proposed that post COVID-19 syndrome may consist of different clinical syndromes comprising of post-intensive care syndrome, post-viral fatigue syndrome, long-term COVID-19 syndrome and chronic illness which may arise from organ damage due to COVID-19, with patients potentially suffering from more than one syndrome and some experiencing different clusters and patterns of symptoms.[9 10] An Italian study following hospitalised patients after discharge noted three different syndromes, separating those related to post-viral chronic fatigue to those due to post-critical illness syndrome or post-traumatic stress disorder. [11 12]

Whilst CYP generally experience less severe COVID-19 than adults, there is emerging evidence that CYP may also develop post-acute symptoms of COVID-19. This condition is distinct from “Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS)” or “Multisystem Inflammatory Syndrome in Children (MIS-C)”, a novel paediatric hyperinflammatory disease phenotype with features of Kawasaki disease and Toxic Shock Syndrome that typically occurs 2-4 weeks after SARS-CoV-2 infection in CYP.[13-18]

Follow-up of adults with COVID-19 has identified multiple persistent and highly variable longer-term symptoms, including fatigue, persistent cough, low-grade fever, headache, chest pain, hair loss, loss of taste and smell among many others. [7,19,20] CYP have also been reported to develop similar symptoms after acute SARS-CoV-2 infection, including fatigue, chronic cough, myalgia, headache, cognitive impairments, dyspnoea and chest pain.[21-23] Because of a lack of consensus about case definitions, estimates of post COVID-19 syndrome prevalence range from very low to very high rates across different studies, and the existing literature is dominated by small, uncontrolled and often single-centre studies, although controlled studies are beginning to emerge. The high prevalence of many somatic symptoms in healthy teenage populations, particularly headache and fatigue,[24] means that uncontrolled studies may inflate post COVID-19 syndrome prevalence, making comparison with non-infected control groups critical. While narrative reviews are beginning to emerge,[25] there is an urgent need for systematic review and meta-analysis of existing literature, particularly focusing on controlled studies.

This systematic review and meta-analysis was undertaken to estimate the prevalence of persistent symptoms following SARS-CoV-2 infection compared with uninfected controls and to identify potential risk factors associated with development of post-COVID symptoms in CYP.

Methods

This systematic review was performed according to PRISMA guidelines; [26,27 28] the protocol was registered with PROSPERO on 01 Mar 2021 (Reference: CRD42021233153).

Eligibility

Studies meeting the following criteria were included:

1. Population: CYP aged ≤19 years with confirmed evidence of SARS-CoV-2 infection (Reverse transcription Polymerase chain reaction (RT-PCR), lateral flow test (LFT) or serology) or probable COVID-19 (clinician defined or suspected COVID-19) who have persistent symptoms as defined by the study authors. We included studies reporting participants from any source but excluded studies where all participants were admitted to intensive care to increase generalisability. Studies including participants of all ages but reporting CYP outcomes separately were eligible.
2. Study type: any study design excluding systematic reviews or other reviews. We included published, preprint and grey literature.
3. Outcomes: the type, prevalence and duration of persistent symptoms in the study population or risk factors for development of persistent symptoms in CYP. We included all symptoms described in each eligible study and included all studies of persistent symptoms regardless of time after infection.

There were no restrictions or limitations on language, date of acceptance or of publications of studies. Google translate was used to translate any non-English publications.

Searches

A systematic search was conducted by the primary reviewer (SAB) from 1st December 2019 to 31st July 2021 in 7 electronic databases (MEDLINE (via OVID), EMBASE (via OVID), CINAHL (via EBSCO), ProQuest Coronavirus Research Database, COVID-19 Living Overview of the Evidence (L-OVE) subset of Episteminokos, Cochrane Covid-19 Study Registry and the World Health Organization (WHO) Covid-19: Global literature on coronavirus disease) and 5 preprint databases (ZBMed's preview database of COVID-related preprints from medRxiv, bioRxiv, ChemRxiv, ResearchSquare and preprints.org). We supplemented searches by a) manual searching of various COVID-19 specialised sources to identify published, unpublished and grey literature (NICE evidence reviews, Up to Date, COVID-END, CADTH COVID-19 pandemic database, Centre for Evidence-based Medicine-Oxford COVID-19 Evidence Service, Cochrane COVID Review Bank, National COVID-19 Clinical Evidence Task Force, John Hopkins centre for humanitarian help, Don't Forget the Bubbles, and BMJ Best Practice COVID-19); cross-examined reference lists in published reviews for relevant studies and

forward search of citations through Google Scholar; searching of reference lists of all included studies; and identifying studies through our professional networks. Each database was searched by using medical subject heading (MeSH) terms and free words including synonyms (in the title and abstract) for the concepts "COVID-19", "children", "adolescents", "long-COVID", "sequelae" and "persistent symptom" (combined with the Boolean logic operation "OR"/ "AND", (Table A2)).

Study selection and data extraction

Titles and abstracts of all studies were screened independently by SAB and independently verified by a second reviewer (SF), with disagreements resolved by consensus or a third reviewer (OS). Data including methods of diagnosis of infection, recruitment source, study characteristics, symptom prevalence and population demographics, were extracted independently by SAB and SB with disagreements resolved by consensus.

Risk of Bias

The methodological quality of included studies was assessed independently by SAB and a second assessor (AZ) using the Newcastle-Ottawa Scale (NOS) for observational studies.[29,30] The Joanna Briggs Institute (JBI) critical appraisal checklist was used for the cross-sectional and case-series studies. [31,32]

Analyses

The primary analysis was restricted to controlled studies: participants with confirmed SARS-CoV-2 infection (cases) were compared with subjects who tested negative for SARS-CoV-2 (controls). We used random effects meta-analyses to examine the pooled risk difference in prevalence of each symptom or symptom combination in cases with confirmed SARS-coV-2 infection compared with controls. Analyses were undertaken in R using the *metafor* commands. Statistical heterogeneity between the results of each study were represented as small if $I^2 < 50\%$, and large if statistical heterogeneity between the results of the studies was $I^2 \geq 50\%$. Given that different patterns and numbers of symptoms were reported by different studies, meta-analysis was only undertaken for symptoms with ≥3 studies providing data. The small number of controlled trials meant that we were unable to undertake meta-regression of study-level moderators nor examine publication bias.

Our secondary analyses examined the pooled prevalence of persistent symptoms only in CYP post-COVID, including uncontrolled studies and positive cases from controlled trials, and used meta-regression to examine study-level factors hypothesised to be associated with prevalence of symptoms. Study-level factors included compositional factors related to study population (mean age; proportion of females; both of which were hypothesised to be associated with higher prevalence), duration of follow-up (hypothesised to be associated with lower prevalence) and study quality factors (study size; risk of bias; recruitment source; degree to which participants had objectively confirmed infection; with higher quality hypothesised to be associated with lower prevalence). Because there were a wide range of reported persistent symptoms (many in only a small number of studies) we conducted meta-analysis and meta-regression only for symptoms where 8 or more studies provided data. Because multiple analyses were undertaken, only associations significant at $p<0.01$ were considered significant. We did not investigate publication bias given the recency of this literature and due to poor performance of standard tests in prevalence studies.[33] Data for symptoms with <8 studies were described but not pooled. Where individual studies identified predictors of symptom prevalence, we reported these descriptively, but data did not allow for pooling of these results.

Results

The search flow is shown in Figure 1. We identified 3,357 articles after removal of duplicates 72 were reviewed in full-text and 22 were included in the review: [34-56] Half of the studies (n=11) were identified through databases and registers and the other half through other methods. Included studies are described in Table 1. Fifteen (68%) were cohort studies, six

(27%) cross-sectional studies and one was a case report. Eight of the 22 studies included population-based control groups. Nine (41%) recruited from a mix of previously hospitalised and non-hospitalised CYP [36,37,43-45,47,50,51,53] nine (41%) recruited from non-hospitalised CYP,[34,35,38,40,41,48,55-57] and four (18%) recruited hospitalised CYP post-discharge.[39,46,49,54] One study of non-hospitalised CYP [36] included CYP from an on-line post COVID-19 syndrome support group of participants who considered their CYP to have post COVID-19 syndrome.

Ten studies were assessed to have high risk of bias, six moderate and six low risk of bias (Table A4). All studies were published during 2020-21 and included participants from high and upper middle income countries; Australia, Faroe Islands, Germany, Italy, Latvia, the Netherlands, Russia, Spain, Sweden, Switzerland, United Kingdom, and the United States. Eight were in pre-print.[34,36,40,43,44,51,55,56] Sample size ranged from 5 to 6,804 CYP with a total of 23,141 participants (median 109). Eleven studies included less than 100 participants. All studies assessed outcomes at >4 weeks after infection (range 28- 324 days), with 15 (68%) assessing outcomes at >12 weeks. Across all studies, 101 symptoms were reported, with 46 symptoms reported in at least 2 studies and 32 symptoms reported in at least 3 studies (Table A5).

Controlled Studies

Five controlled studies provided sufficient data for meta-analyses. Four were community studies and one included a mix of hospitalised and non-hospitalised CYP and hospital recruitment. All were rated as good (four studies) or fair (one study) quality. Across the five studies, all cases had objective evidence of SARS-CoV-2 infection with one study using self-reported evidence of infection and four studies reporting evidence where results were independently verified.

Meta-analyses were undertaken for 14 symptoms within the controlled studies. Four or more controlled studies provided data on cognitive difficulties, headache, abdominal pain, cough, myalgia and fatigue, with forest plots for these meta-analyses shown in Figure 2. There were significantly higher pooled estimates of proportions of symptoms in the cases with confirmed SARS-CoV-2 infection for cognitive difficulties (pooled risk difference 3%

(95% CI 1, 4)) and headache (5% (1, 8)) but not for abdominal pain, cough, fatigue or myalgia. Heterogeneity was low for cognitive difficulties, abdominal pain and cough but high for headache, fatigue and myalgia.

Pooled estimates for symptoms where only three studies provided data are shown in Figure 3 (insomnia, loss of smell, diarrhoea, sore throat, fever, dizziness, dyspnoea and sore eyes). Pooled risk differences were significant for loss of smell (8%, (2, 15)), sore throat (2% (1, 2)) and sore eyes (2% (1, 3)) but not for insomnia, diarrhoea, fever, dizziness or dyspnoea. Heterogeneity was low for insomnia, diarrhoea, sore throat and eyes and fever but high for loss of smell, dizziness and dyspnoea.

Only two studies provided data on multiple persistent symptoms and were, therefore, not eligible for meta-analysis. Both studies [48,58] found no difference in the proportions of cases and controls with 1-2 persistent symptoms. One study[58] which involved teenagers completing questionnaires about their own health status, found a significantly higher proportion of cases than controls had three or more persistent symptoms (risk difference 14% (12, 16)), whilst another study [48], which used proxy reporting of symptoms by parents, did not find a significant difference (5% (0, 10)).

Other persistent symptoms were reported by <3 studies and therefore not included in the meta-analyses. These included loss of appetite, skipping meals, nausea, vomiting, constipation, problem swallowing, joint pain, chest pain/tightness, nasal congestion, tiredness/weakness, chills, heart palpitations, earache/ringing in the ear, tingling feeling, seizures, altered taste, hypersomnia, listlessness, depression, sadness, mood swings, anxiety, rash, red welts, blisters/skin peeling, hoarse voice, problem communicating, blurred vision, twitches, and hair loss.

Prevalence and predictors of symptoms in post-COVID CYP

Across all study types, 10 symptoms had data from ≥8 studies allowing meta-analysis and meta-regression: cognitive difficulties, headache, fatigue, fever, myalgia, cough, dyspnoea, abdominal pain, diarrhoea and anosmia / altered sense of smell.

Seventeen studies provided data for these analyses: Five studies included SARS-CoV-2 positive cases from controlled studies and 12 were uncontrolled studies. Seven were community studies, two had hospital recruitment of cases and eight had a mix of hospitalised and non-hospitalised CYP recruitment.

Table 2 shows pooled prevalence (95% CI) of symptoms in SARS-CoV-2 positive CYP, alongside findings from meta-regressions for hypothesised moderators for each meta-analysis. Pooled prevalence of symptoms ranged from 15% (diarrhoea) to 47% (fatigue), with high heterogeneity across all symptom analyses. Meta-regression of study participant characteristics showed that higher study age was associated with higher prevalence of all symptoms with the exception of lower prevalence of cough, and that a higher proportion of female participants was associated with higher prevalence of fatigue, headache, myalgia, diarrhoea, loss of smell and dyspnoea and lower prevalence of cough and abdominal pain. Meta-regression analyses of study characteristics found that some study quality markers (higher proportion of objectively confirmed cases; low risk of bias; community compared with a mix of hospitalised and non-hospitalised CYP recruitment) were consistently associated with lower prevalence of all symptoms, except loss of smell and cognitive symptoms. However, study size was inconsistently associated with symptom prevalence.

The duration of persistent symptoms was reported in 13 studies [23,36,38,41,43,45,50,53,55,59-62] with a median of 125 days (IQR 99-231) after acute SARS-CoV-2 infection. In meta-regression, longer follow-up duration was associated with lower prevalence of cough, headache, cognitive problems, abdominal pain but higher prevalence of fever, fatigue, myalgia, diarrhoea, loss of smell and dyspnoea.

Small/limited number of available studies at present meant that we were unable to undertake meta-analysis of number of persistent symptoms nor of a range of other symptoms. These symptoms are reported in Table A6.

Risk Factors

Few studies examined risk factors associated with persistent post-COVID symptoms in CYP. Osmanov et al. reported that persistent symptoms were more common among CYP aged 6-11 (odds ratio 2.74, 95% CI, 1.37 to 5.75) and those 12-18 years (OR 2.68, 95% CI, 1.41 to

5.4) compared to those aged <2 years, as well as among CYP with a history of allergic diseases (OR 1.67, 95% CI, 1.04 to 2.67).[61] Molteni et al. reported that older CYP (12-17 years) were more likely to manifest symptoms ≥28 days in comparison with younger CYP (5-11 years) (5.1% vs. 3.1%).[45] Miller et al. reported that persistent symptom prevalence was higher in females (OR 1.79 [95% CI, 1.07 to 2.99]), teenagers (OR 2.67 [95% CI, 1.56 to 4.57]) and CYP with long-term health conditions (OR 2.95 [95% CI, 1.59 to 5.45]).[60] Females also reported a consistently higher prevalence of neurocognitive and pain symptoms compared to males in Blankenburg et al., with age being positively correlated with nearly all neurocognitive and pain symptoms.[34] Stephenson et al. reported that for both SARS-CoV-2-positive and SARS-CoV-2-negative CYP, in those assigned to the latent class with "multiple symptoms" at three months, being female, older and having poorer physical and mental health before COVID-19 were important risk factors.[58]

Discussion

In this comprehensive systematic review and meta-analysis of 22 studies, we identified 101 symptoms reported to be persistent after SARS-CoV-2 infection in CYP, across cardiovascular, respiratory, gastrointestinal, musculoskeletal, skin and nervous systems as well as general somatic symptoms. Our analyses focused on persistence of individual symptoms and combination of symptoms where these were reported by multiple studies. Data were sufficient for us to examine 14 of the most common symptoms in controlled studies and 10 symptoms in uncontrolled analyses. The lack of an agreed case definition means that we were unable to comment on the prevalence of post COVID-19 syndrome(s) in CYP.

The majority of the included studies were of poor quality, predominantly uncontrolled and retrospective, and open to selection bias. There are a number of reasons why symptoms reported in many of these studies may not be specific to SARS-CoV-2, including the high prevalence of somatic symptoms such as fatigue and headache in healthy CYP, the overlap of symptoms such as fatigue, poor concentration and headache, with mental health symptoms (which rose during the pandemic), and potential attribution bias. Our primary analysis therefore focused on controlled studies and found that the frequency of the majority of reported persistent symptoms was similar in SARS-CoV-2 positive cases and controls. Risk differences for abdominal pain, cough, myalgia, insomnia, diarrhoea, fever, and dizziness were each very close to zero and not significant. However, loss of smell occurred in 8% more cases than controls, as did headaches (5%), cognitive difficulties (3%) and sore throat and eyes (2% each). Fatigue occurred in 7% more cases than controls although confidence intervals included zero. Combinations of persistent symptoms could not be included in meta-analyses but the two studies that considered this found no difference between cases and controls in the proportions with 1-2 persistent symptoms. Estimates of the excess proportion of cases with 3 or more symptoms were 5% and 14% in these studies.

The excess in the proportion of cases with specific symptoms compared to controls was much lower than the pooled estimates of symptom prevalence in the secondary analyses of cases alone. This was true across all symptoms studied. Pooled estimates were particularly high for fatigue (47%) and headache (35%), approximately 7-fold higher than in controlled studies, highlighting the importance of including a control group.

Our meta-regressions, whilst performed at study level rather than at the level of individual participants, suggested that older age and female sex were associated with increased risk of persistent symptoms. Higher study quality, community recruitment and test-confirmed diagnosis of infection were each strongly and consistently associated with lower prevalence, highlighting the importance of scientific quality in investigating emerging phenomena such as post-COVID syndromes.

Comparison with the literature

One previous narrative review noted the high prevalence of multiple symptoms in the majority of studies of persistent post-COVID symptoms, however this study did not undertake meta-analysis of symptom prevalence.[25] We found that somatic or constitutional symptoms such as fatigue (47%) and headache (35%) were amongst the most commonly reported symptoms in CYP post-COVID. This is consistent with other systematic reviews in adults and CYP,[20,25,63,64] yet in controlled studies that accounted for high background prevalence in non-infected CYP, we found that the excess in cases over controls was much lower at 5% (headache) and 7% (fatigue). It is important to note that post-infection fatigue appears to be common in CYP with post COVID-19 syndrome and have also been reported after other human coronaviruses such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS) as well as Epstein-Barr, Dengue, Zika, Ebola and Chikungunya viruses.[65,66] Headache is a commonly reported neurological symptom in acute SARS-CoV-2 infection and can persist after acute infection.[67]

We found evidence that that female sex, underlying comorbidities, and increasing age were associated with increased risk of persistent symptoms after SARS-CoV-2 infection in CYP. For sex this is consistent with a higher risk observed with other post-viral syndromes[70] and in adults with post COVID-19 syndrome. [25,64,71]

Limitations

Our findings are subject to a number of limitations. Low study quality is discussed above. The majority of the meta-analyses had high heterogeneity, almost certainly due to both measurement issues across studies and to differing samples, recruitment strategies and follow-up times. Because of this we used a random effects meta-analysis to take account of unmeasured between-study factors. Our findings were limited by lack of data for many symptoms, particularly combinations of symptoms. Very few studies provided data on the impact of symptoms on daily functioning amongst CYP. We were unable to assess publication bias; however, this is likely to play less of a role in a highly topical new area.

Some studies were open to misclassification bias, including suspected cases without laboratory confirmation of diagnosis. Definitions and reporting of symptoms differed across studies, and whilst we categorized similar symptoms, together this may have introduced bias. Studies used a mix of child or parent reporting, and some studies had permissive inclusion of symptoms, which may be persistent following acute infection, new-onset of symptoms days to weeks after acute infection, worsening of pre-existing symptoms prior to SARS-CoV-2 infection, as well as waxing and waning of symptoms during follow-up after acute infection. As all participants were aware of their infection status, attribution bias is also likely to have influenced symptom reporting, as seen in other infections.[72]

Almost all studies (95%) were from high income countries, limiting generalisability for low- and middle-income countries. The median duration of follow-up after COVID-19 symptom onset was 120 days (IQR 56.3, 187.1) and ranging between 28 and 324 days between studies. This led to substantial disparity in the timelines for symptom onset and assessment in our systematic review and likely influenced the combinability of our estimates of prevalence and symptom duration.

Implications

Persistent symptoms of loss of smell, headaches, cognitive difficulties and sore throat and eyes each occur in 2 to 8% more CYP after SARS-CoV-2 infection than in those without infection. Two large controlled studies suggest that 5-14% may have multiple persistent symptoms 4 weeks or more after acute infection. However, the majority of the 14 most commonly symptoms reported in CYP post-COVID were no more common in those with documented SARS-CoV-2 infection compared with those without infection. These findings suggest that persistent symptoms occur both singly and in clusters in CYP after SARS-CoV-2 infection, but prevalence is much lower than suggested by many low-quality uncontrolled studies.

Our findings confirm the urgent need to provide health and education services for those with significant post-COVID symptoms and our data provide estimates for planning these. Our review also shows the paucity of data on many aspects of post-COVID symptoms in CYP, particularly on the pathophysiology of symptoms and the functional limitations linked with reported symptoms. Further work is needed to understand frequency of particular clusters of symptoms and severity and functional limitation related to these, in order to inform both preventive and treatment strategies. There is also a need to understand the relationship of mental health problems during the pandemic to symptom clusters in order to prioritise healthcare services and resources to support and minimise the consequences of the pandemic in the CYP population.

Our findings highlight the critical importance of a control group in this area of study. Additional research priorities in developing treatment programs will need to be targeted to symptoms associated with SARS-CoV-2 infection, rather than symptoms which may be attributable to pandemic societal pressures. We hope that this work will act as a stimulus for the design of more high quality prospective controlled studies in this area. Only with these can we really inform the global policy conversation around the health of CYP during the pandemic.

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Conflicts of Interest:

SAB, RS, SDB, AXDZ, LLO, SNL, BLDS, RMV and OVS have no conflicts of interest.

TJS is the Chair of the Health Research Authority for England who reimburse his university for his time. He is not paid personally. He has recused himself from research studies in which he is personally involved and which require ethical approval from the HRA.

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Data sharing:

No individual patient level data was used during this analysis. Data extracted for this study, including study protocol, individual assessments of study quality and risk of bias in addition to analytical code will be made available following publication. Requests for data and code can be made to the corresponding author, outlining specific data needs, analysis and dissemination plans.

Figure 1: PRISMA 2020 flow diagram for included studies

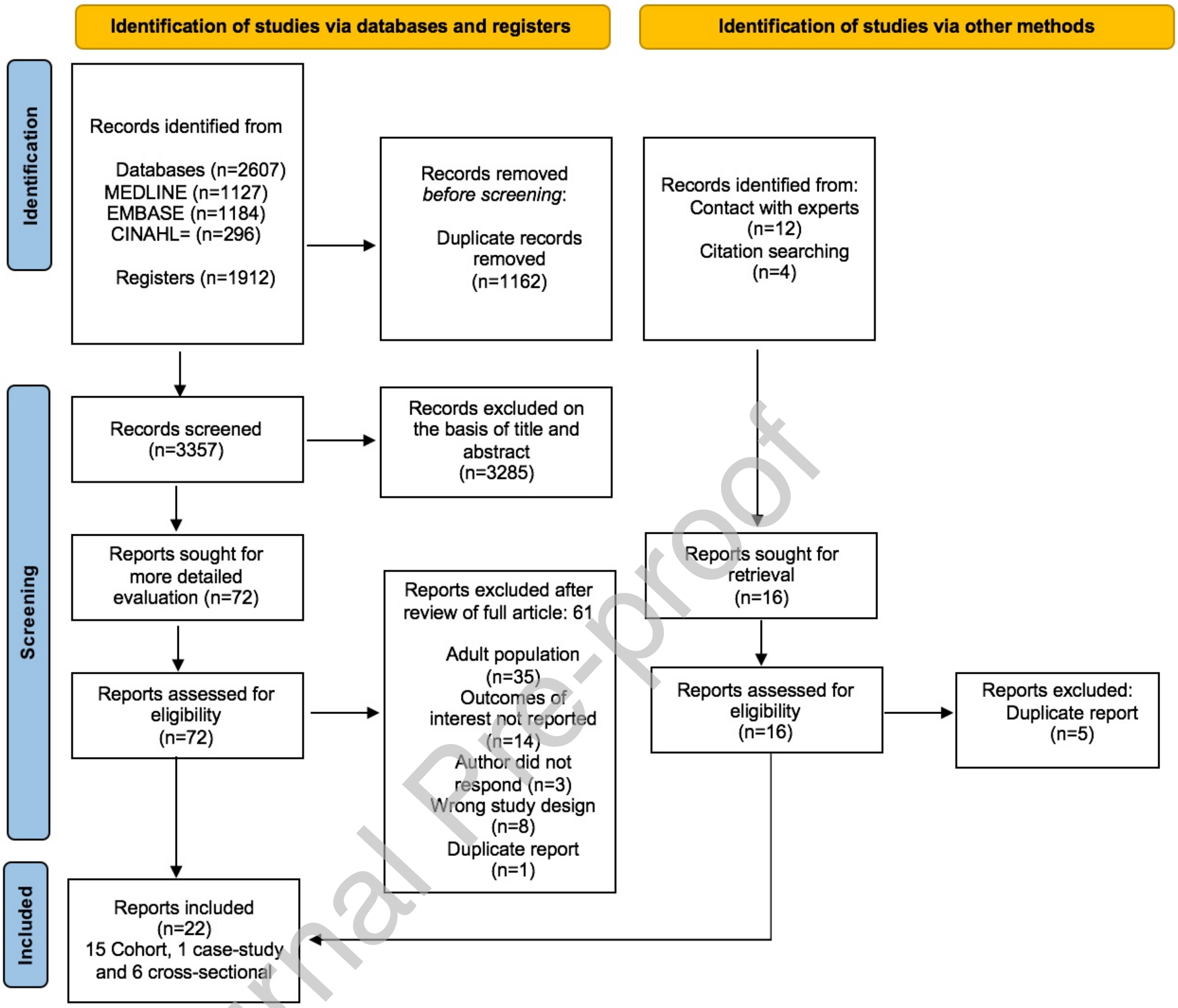

Table 1: Characteristics of Included Studies

Study ID (author)	Country	Sample size (n)	Study Design	Age (years) mean±SD median (IQR) or [Range]	Sex (% Female)	Baseline severity of COVID-19	Diagnostic Criteria	Duration of Follow-up	Pre-existing Comorbidities	Inclusion Criteria
Blankenburg, [34]	Germany	188 Seropositive	Cohort (Preprint)	Seropositive= 15 (14-17) [Range:10-35]	55% Seropositive	NR	Serology (100%)	NR	NR	Grade 8-12 students in 14 secondary schools with seroprevalence assessment
Brackel, [35]	Netherlands	89	Cross-sectional	13 (9-15)	NR	18% admitted to hospital	RT-PCR 52.8% Serology 34.8% serology CD 38.2% Suspected 9 %	≥12 weeks after symptom onset	NR	CYP referred to pediatricians across hospitals in Netherlands for long-COVID assessment
Buonsenso a, [36]	UK	510	Cross-Sectional (Preprint)	10.3±3.8	56.3%	12.2% asymptomatic 74.1% managed at home, and 9.4% went to hospital but were not admitted	RT-PCR-27.7% LFT-0.8% CD-30.6% Suspected 41%	>4 weeks after symptom onset	43.7% had no pre-existing comorbidities.	CYP with signs persisting for more than 4 weeks included. Self-selected from online patient group.

Study ID (author)	Country	Sample size (n)	Study Design	Age (years) mean±SD median (IQR) or [Range]	Sex (% Female)	Baseline severity of COVID-19	Diagnostic Criteria	Duration of Follow-up	Pre-existing Comorbidities	Inclusion Criteria
Buonsenso b, [37]	Italy	129	Cross-Sectional	11±4.4	48.1%	25.6% asymptomatic 74.4% symptomatic 4.7% hospitalised 2.3% ICU admission	All microbiologically confirmed COVID-19	162.5 ±113.7 days	10.1%, neurological disease, 3.9% asthma, 4.7% skin problems	CYP ≤18 years old diagnosed with microbiologically confirmed COVID-19
Chevinsky, [38]	USA	305 inpatients 2,368 outpatients	Cohort	Range [≤1-17]	43.6% inpatient 50.5% outpatient	NR	CD (100%)	[Range: 31-120] days	NR	Adults and CYP aged <18 years identified from all payer databases including inpatient and outpatient data from April-June 2020
Denina, [39]	Italy	25	Cohort	Median: 7.75 [Range: 0.4-15]	48%	28% mild 56% moderate 16% severe	Serology or RT-PCR	4 months	1 cystic fibrosis 1 congenital heart disease	CYP admitted to paediatric COVID-19 dedicated clinic from March 1 to June 1, 2020

Study ID (author)	Country	Sample size (n)	Study Design	Age (years) mean±SD median (IQR) or [Range]	Sex (% Female)	Baseline severity of COVID-19	Diagnostic Criteria	Duration of Follow-up	Pre-existing Comorbidities	Inclusion Criteria

Study ID (author)	Country	Sample size (n)	Study Design	Age (years) mean±SD median (IQR) or [Range]	Sex (% Female)	Baseline severity of COVID-19	Diagnostic Criteria	Duration of Follow-up	Pre-existing Comorbidities	Inclusion Criteria
Dobkin,[43]	USA	29	Cohort	13.1±3.9 [Range: 4-19]	58.6%	93.1% symptomatic 13.8% hospitalised 3.4% delayed MIS-C	RT-PCR or positive confirmed close household contacts with positive SARS-CoV-2 testing	3.2 ± 1.5 months [Range: 1.3-6.7] months	62.1% overweight /obese 38% asthma	CYP referred to Pulmonary Clinic at the Children's Hospital of Philadelphia with history of SARS-CoV-2 positivity or confirmed close household contact
Knoke, [44]	Germany	73 SARS-CoV-2 + 45 SARS-CoV-2 -	Cross-sectional	10.82±-3.25	52%	35.6% symptomatic, 63% asymptomatic	Serology or RT-PCR	2.59 [Range 0.4–6.0] months	23.3% pulmonary disease	COVID-19 positive CYP from 5-18 years. CYP with negative antibodies for SARS-CoV-2 and no other evidence of SARS-CoV-2 infection served as controls
Ludvigsson, [41]	Sweden	5	Case report	12 [Range: 9-15]	80%	100% CYP mild disease	Probable COVID-19. All 5 CYP had been diagnosed with COVID-19 by their physician	6-8 months	1 with asthma	Inclusion of CYP whose parents contacted the study author

Study ID (author)	Country	Sample size (n)	Study Design	Age (years) mean±SD median (IQR) or [Range]	Sex (% Female)	Baseline severity of COVID-19	Diagnostic Criteria	Duration of Follow-up	Pre-existing Comorbidities	Inclusion Criteria
Miller, [40]	England and Wales	4678 (175 with evidence of past or present SARS-Cov-2 infection)	Cohort (Preprint)	Age <2: 7.0% Age 2-11 years: 53.9% Age 12-17 years: 39.1%	40.6%	NR	RT-PCR 100%	≥28 days	10.2% reported long term health conditions	CYP aged ≤17 years at enrolment History of SARS-CoV-2 infection
Molteni, [45]	UK	1734 RT-PCR + 1734 RT-PCR -	Cohort	13 (10-15) [Range: 5-17]	50.2% COVID-19 50.1% Control	2.1% of SARS-CoV-2 + visit to hospital 1.5% of SARS-CoV-2 - visit to hospital	RT-PCR 100%	≥28 days	12.8%: asthma In SARS-CoV-2 positive 13.2%: asthma In SARS-CoV-2 negative	CYP ≤18 years old testing positive for SARS-CoV-2 and negative control CYP ≤18years old testing negative for SARS-CoV-2 from a mobile smartphone application
Nogueira López, [42]	Spain	8	Letter to Editor (reporting a Retrospective Cohort study)	11.8 (9.82-13.9)	50%	NR	RT-PCR 25% 87.5% Suspected	52.5 (25–60.5) days	12.50%	CYP ≤18 years old with confirmed or probable diagnosis of COVID-19
Osmanov, [46]	Russia	518	Cohort	10.4 (3–15.2)	52.1%	All hospitalised 2.7% severe disease requiring ventilation	RT-PCR 100%	256 days (223-271)	No comorbidities: 55.3%. One comorbidity: 27.4%. ≥ two comorbidities 17.3%	CYP (≤18 years old) admitted with confirmed COVID-19 to hospital between April 2, 2020, and August 26, 2020

Study ID (author)	Country	Sample size (n)	Study Design	Age (years) mean±SD median (IQR) or [Range]	Sex (% Female)	Baseline severity of COVID-19	Diagnostic Criteria	Duration of Follow-up	Pre-existing Comorbidities	Inclusion Criteria
Petersen, [47]	Faroe Islands	21	Cohort	[Range: 0-17]	NR	None hospitalised	RT-PCR 100%	125± 17 days [Range: 45-153]	NR	COVID-19 confirmed patients diagnosed by RT-PCR March 3,2020 and April 2,2020
Radtke, [48]	Switzerland	Seropositive 109 Seronegative 1246	Cohort	[Range: 6-16]	Seropositive group: 53% Seronegative group: 54%	No hospitalisation reported in the seropositive group	Serology 100%	>4 weeks >12 weeks 6-month follow-up	89% with no comorbidities Seropositive group 72% no comorbidities seronegative group	CYP who tested positive for SARS-CoV-2 antibodies and CYP who tested negative for antibodies in October/November 2020 from primary or secondary schools
Rusetsky, [49]	Russia	79	Cross-sectional	12.9±3.4	53.2%	NR	RT-PCR 100%	60 days after hospital discharge	NR	CYP ≥5 years with SARS-CoV-2 infections confirmed by RT-PCR
Sante, [75]	Italy	12 long-COVID 17 Recovered group	Cross-sectional	Long-COVID group 10.3±4.5 Recovered group 7.7±5.5	Long-COVID group-33.3% Recovered group-35.5%	29.4% recovered group	100% RT-PCR	98.5 ± 41.5 days	Long-COVID group: 25.0% Recovered group: 17.6%	CYP with microbiologically confirmed (with PCR on nasopharyngeal swab) acute COVID-19

Say, [50]	Australia	12	Cohort	3 (1–8)	47%	58% mild disease 36% asymptomatic 5% moderate disease 8% hospitalised	"Children who tested positive for SARS-CoV-2"	[Range 3-6 months]	25%	CYP aged ≤18 years who tested positive for SARSCoV-2 in hospital or externally
Smane, [53]	Latvia	30	Cohort	9.2±5.2	43%	Most CYP had mild to moderate illness. 16.6% CYP were hospitalised	Antigen test using real time PCR for COVID-19	101 ± 7 days	Comorbidities in 23%	All hospitalised and non-hospitalised CYP (0-17) with two negative test results for SARS-Cov-2 24 hours apart
Stephenson, [58]	England	3065 Test-positives 3739 Test-negatives	Cohort (Preprint)	Age: 11-15 (56.8%) Age: 16-17 (43.1%)	63.5% Test-positives 62.9% Test-negatives	64.6% asymptomatic Test-positives 91.7% asymptomatic Test-negatives	RT-PCR 100%	14.9 weeks (13.1-18.9)	NR	11-17-year old's with laboratory-confirmed SARS-CoV-2 infection contacted from a database of test results held by Public Health England from January-March 2021

Study ID (author)	**Country**	**Sample size (n)**	**Study Design**	**Age (years) mean±SD median (IQR) or [Range]**	**Sex (% Female)**	**Baseline severity of COVID-19**	**Diagnostic Criteria**	**Duration of Follow-up**	**Pre-existing Comorbidities**	**Inclusion Criteria**
Sterky, [54]	Sweden	55	Cohort	[Range: 0-18]	58%	9 fulfilled the criteria for (MIS-C)	RT-PCR positive for SARS-CoV-2	219 days (123-324)	35% had chronic illness at admission	CYP aged 0-18 who were admitted to one of the two

						2 of these required intensive care 38% admitted for dehydration 35% for infection observation 23% for inhalations				paediatric hospitals in the Stockholm Region and RT-PCR positive for SARS-CoV-2
Zavala, [56]	UK	Case: 472 Control: 387	Cohort (Preprint)	10 (6, 13)	Cases: 50.2% Control: 47%	Cases: 67.79% Symptomatic, 32.20% asymptomatic Controls: 39.79% symptomatic 60.2% asymptomatic	RT-PCR 100%	>1 month	6.6% had one or more co-morbidities	CYP aged 2-16 years who had an upper respiratory tract swab for SARS-CoV-2 RT-PCR during the first week of January 2021 in England

Data are means ± standard deviations, medians with interquartile ranges (IQR) or [ranges]. Abbreviations: RT-PCR: Positive reverse transcription polymerase chain reaction; NR: not reported; CD: Clinical Diagnosis, LFT: Lateral Flow Test; MIS-C: Multisystem Inflammatory Syndrome in Children; ICU: Intensive Care Unit

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Figure 2. Meta-analyses of risk difference in symptom prevalence between cases and control populations in controlled studies: analyses including 4 or more studies

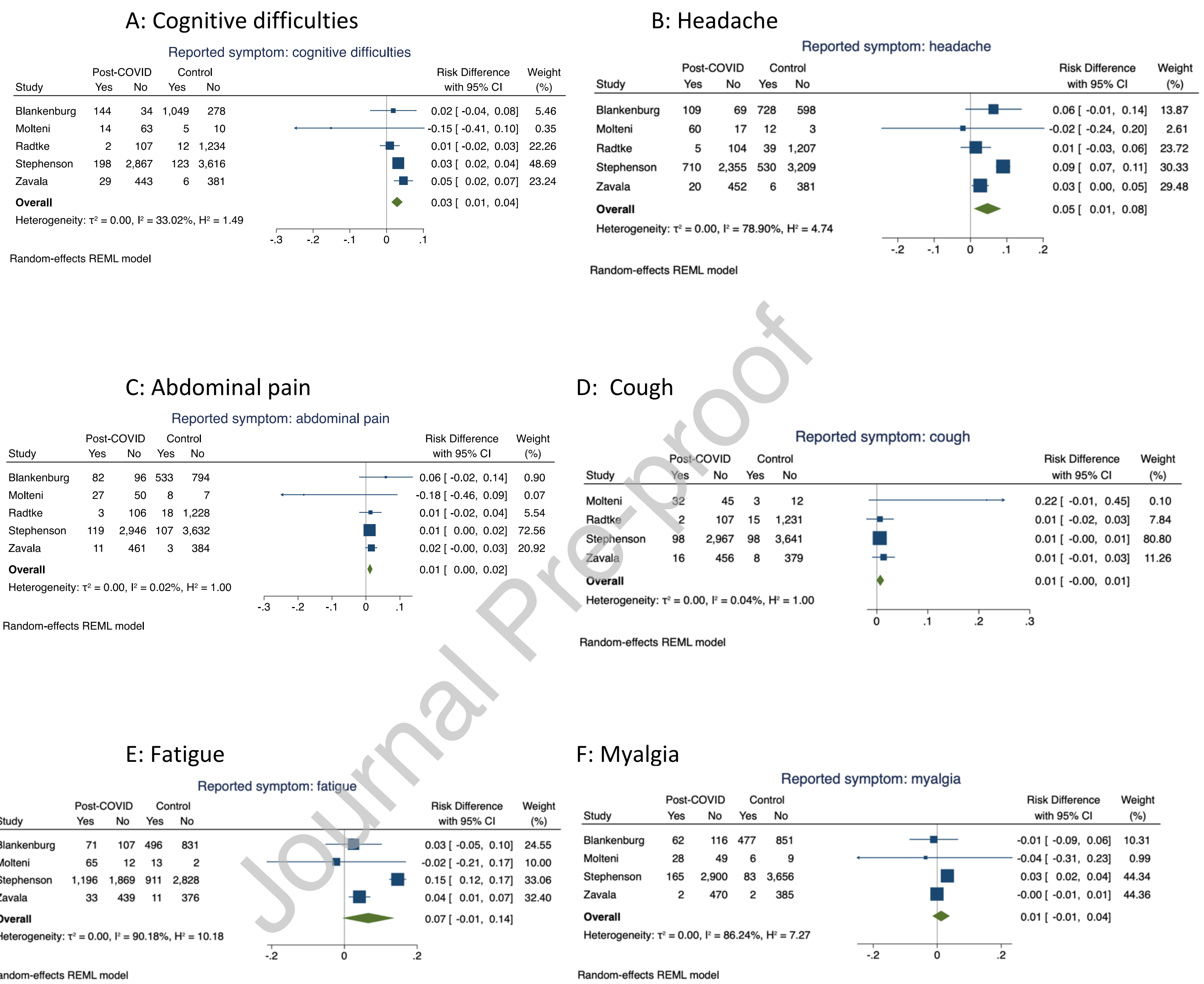

Figure 3. Meta-analyses of risk difference in symptom prevalence between cases and control populations in controlled studies: analyses including 3 studies

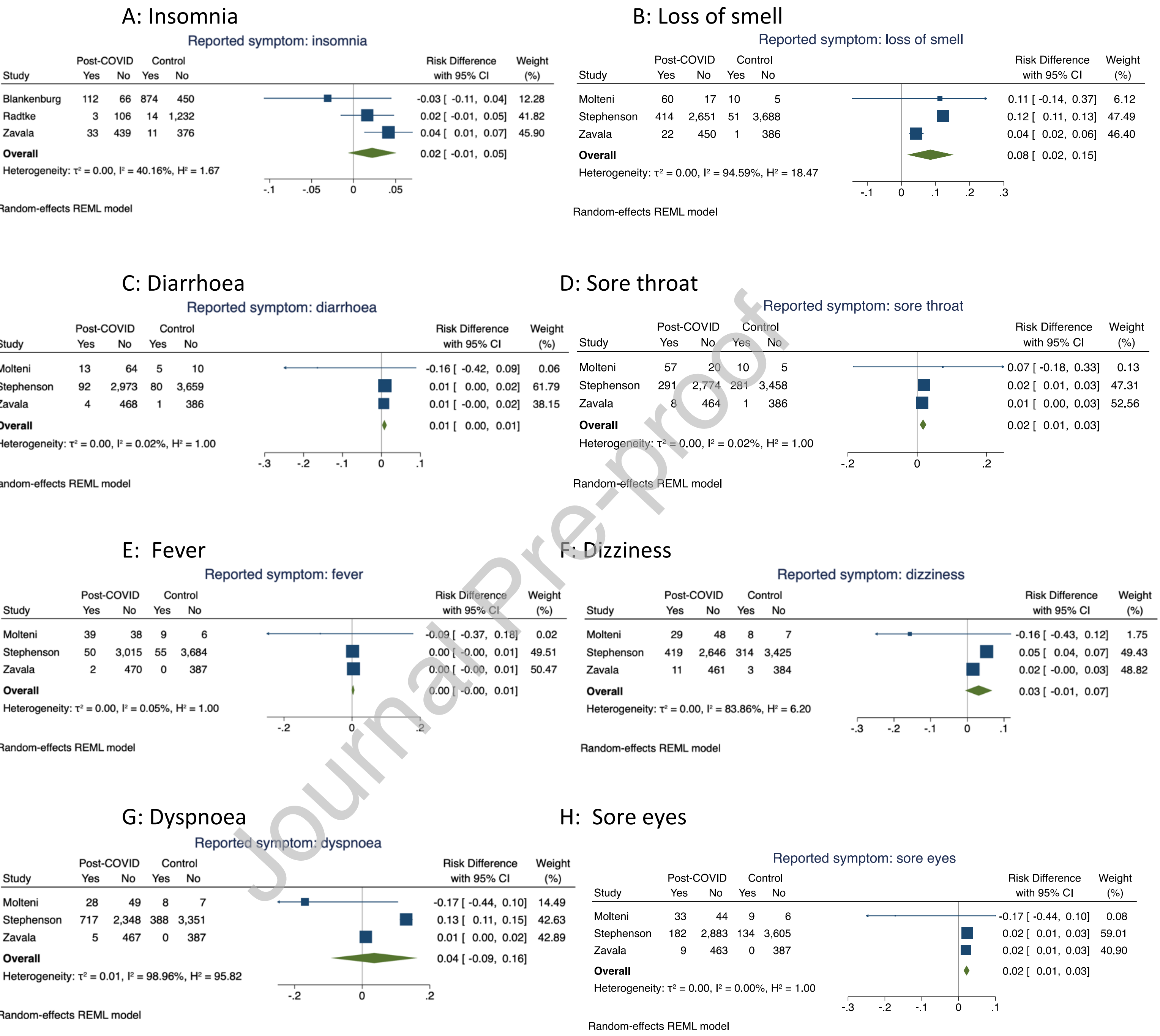

Table 2. Pooled estimates and meta-regression coefficients for uncontrolled analyses of symptom prevalence

	Pooled estimates			Meta-regression					Risk of bias: Reference=Low		
	Prevalence	N	n	Age	Female proportion	Study size(/100)	Follow-up (months)	Community versus mixed recruitment	Moderate risk	High risk of bias	% confirmed diagnosis
Cough	17(28, 87)	13	4656	0.99(0.98,0.99)*	0.99(0.997,0.99)*	0.999(0.998,0.999)*	0.99(0.99,1.00)	0.85(0.83,0.87)*	0.99(0.97,1.01)	1.14(1.11,1.17)*	0.995(0.994,0.996)*
Fever	18(5, 32)	8	4241	1.02(1.01,1.03)*	1.001(1.00,1.001)	1.000(0.999,1.000)	1.00(1.00,1.001)	0.74(0.71,0.77)*	1.02(0.98,1.05)	1.33(1.28,1.38)*	0.994(0.993,0.995)*
Fatigue	47(32, 62)	15	4817	1.09(1.07,1.10)*	1.014(1.012,1.016)*	1.002(1.001,1.003)*	1.02(1.01,1.03)*	0.74(0.72,0.76)*	1.12(1.08,1.17)*	1.45(1.40,1.49)*	0.988(0.987,0.989)*
Headache	35(19, 51)	13	4795	1.12(1.11,1.14)*	1.009(1.008,1.011)*	1.001(1.001,1.002)$^{\Psi}$	0.99(0.98,0.99)$^{\Psi}$	0.66(0.64,0.68)*	1.16(1.11,1.20)*	1.56(1.51,1.61)*	0.986(0.985,0.986)*
Cognitive difficulties	26(8, 44)	10	4264	1.15(1.14,1.16)*	1.000(0.999,1.001)	0.999(0.998,1.000)	0.99(0.98,0.99)*	0.95(0.91, 1.000)	1.44(1.39,1.49)*	0.96(0.94,0.98)*	0.99(0.986,0.993)*
Myalgia	25(11, 40)	10	4665	1.10(1.08,1.11)*	1.004(1.003,1.005)*	1.001(1.001,1.002)*	1.01(1.01,1.02)*	0.65(0.63,0.67)*	1.20(1.16,1.25)*	1.28(1.25,1.31)*	0.985(0.984,0.986)*
Abdominal pain	25(9, 42)	10	4762	1.08(1.06,1.09)*	0.998(0.997,0.999)*	0.998(0.997,0.998)*	0.98(0.98,0.99)*	0.80(0.78,0.81)*	1.05(1.03,1.08)*	1.59(1.54,1.64)*	0.983(0.982,0.984)*
Diarrhoea	15(4, 26)	8	4475	1.05(1.03,1.07)*	1.001(1.00,1.002)	1.000(0.999,1.001)	1.00(1.00,1.007)	0.93(0.91,0.95)*	1.01(0.98,1.03)	1.28(1.24,1.32)*	0.991(0.99,0.992)*
Loss of smell	18(2, 34)	9	3986	1.00(0.99,1.01)	1.004(1.003,1.006)*	1.003(1.002,1.004)*	1.01(1.01,1.02)*	0.95(0.92,0.98)$^{\Psi}$	0.91(0.89,0.93)*	1.05(0.99,1.12)	1.007(1.005,1.009)*
Dyspnoea	43(18, 68)	8	3882	1.28(1.26,1.30)*	1.021(1.019,1.022)*	1.007(1.006,1.008)*	1.05(1.05,1.06)*	0.50(0.47,0.53)*	1.67(1.53,1.82)*	1.25(1.21,1.30)*	0.99(0.988,0.992)*

N= number of studies, n=pooled total sample size, $^{\Psi}p<0.01$, *p<0.001

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6-7 Supp Info Table A1 Table A2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supp Info Table A2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6-7

Section and Topic	Item #	Checklist item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7 Supp Info Table A4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp Info Table A4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supp Info Table A6

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7 Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-12
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-12 15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9-12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-14
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	17
Competing interests	26	Declare any competing interests of review authors.	17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supp Info and 17